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Heterogeneity of resting and hyperemic myocardial blood flow in healthy humans

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Abstract

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Keywords: Adenosine; Blood flow; Coronary circulation

1. Introduction

A number of recent studies using positron emission tomography (PET) have demonstrated that resting myocardial blood flow (MBF) to hibernating myocardium is often within normal limits [1–4]. This is in contrast with other reports showing that resting flow to hibernating myocardium is reduced [5]. Part of the problem lies in the fact that resting MBF is heterogeneous in both normal humans and animals [6–14]. As a consequence, it is difficult to define the range and particularly the lower limit of normal resting MBF. In addition, the small sample size of most published reports could contribute, at least in part, to this heterogeneity. Studies of MBF in larger populations might help to overcome this limitation.

Several techniques are available for measuring coronary or myocardial blood flow in humans, including Doppler catheterization, quantitative coronary arteriography, thermodilution, and measurement of inert tracer clearance [15]. However, most methods are invasive and affected by serious limitations [15]. Noninvasive assessment of MBF may be performed with either single photon emission computerized tomography (SPECT) or PET, but the physical limitations of SPECT do not permit absolute quantitation of MBF. On the other hand, PET overcomes some of these limitations by providing superior resolution and accurate attenuation and partial volume corrections, thus enabling reproducible absolute quantification of regional

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MBF [16,17]. The aim of this study was therefore to measure absolute baseline and hyperemic MBF in a large group of normal volunteers using PET with oxygen-15 labeled water ($H_2^{15}O$).

2. Methods

2.1. Study population

We have accumulated MBF data in a large group of normal volunteers from a number of different studies. The current retrospective series was produced using this database. The study population consisted of 169 healthy volunteers (38 women and 131 men) aged 21–86 years (mean±S.D., 46±12 years). Volunteers were recruited by public advertising or from hospital staff. Volunteers over the age of 80 years were recruited from a ballroom dancing class. The mean age of females was significantly higher than that of males (54±13 vs. 44±11 years; $P<0.0001$). All subjects gave no history of cardiac or pulmonary disease, hypertension, hyperlipidemia, diabetes, or smoking. In 76 subjects a lipid profile was also obtained and was within normal limits (mean total cholesterol 4.5±0.4, range 1.9–5.3 mmol/l). All subjects gave history of normal effort tolerance, had a normal cardiac and pulmonary examination, and a normal resting electrocardiogram. Based on these findings, all participants had a low clinical probability of coronary artery disease [18].

2.2. Study protocol

The study protocol was approved by the Research Ethics Committee of Hammersmith Hospital and radiation exposure was licensed by the United Kingdom Administration of Radioactive Substances Advisory Committee (ARSAC). The study conforms with the principles outlined in the Declaration of Helsinki. All participants gave informed and written consent prior to the study.

Subjects were investigated by means of PET for the quantification of MBF (1) at baseline ($n=169$) and (2) during hyperemia ($n=160$) induced by standard intravenous dipyridamole (0.56 mg/kg infused over 4 min, $n=83$) or adenosine (140 μg/kg/min, $n=77$). Only dipyridamole was used in females ($n=36$), and either dipyridamole ($n=47$) or adenosine ($n=77$) was used in males. This was because the female volunteers were part of the control group for specific studies in which only dipyridamole was used. In a subgroup of 21 male subjects, repeated measurements of MBF were performed at rest and during adenosine-induced hyperemia. The two baseline studies were timed to be exactly 20 min apart, and the two hyperemic studies were also exactly 20 min apart.

For the measurement of MBF, a slow bolus of $H_2^{15}O$ was injected 2 min after the beginning of adenosine infusion or 90 s after completion of dipyridamole infusion. The timing of the $H_2^{15}O$ injection and scan for the dipyridamole hyperemic MBF was based on our previous observation [19] that, on average, peak coronary hyperemic response to dipyridamole occurs 8 min after the start of infusion or, 4 min following the end of the dipyridamole infusion. The $H_2^{15}O$ infusion was therefore timed so that its peak coincided with the peak action of dipyridamole. Blood pressure was recorded by Dynamap (Critikon, Tampa, FL, USA) at baseline and at 1-min intervals during adenosine or dipyridamole infusion. The heart rate and rhythm were monitored continuously throughout the procedure by a microprocessor-driven electrocardiographic recorder (Sirecust 341, Siemens, Germany). One set of blood pressure and heart rate was recorded to coincide with the peak action of the $H_2^{15}O$ bolus and pharmacologic stress agent. A 12-lead electrocardiogram (Marquette, Milwaukee, WI, USA) was obtained at baseline and every minute of the adenosine or dipyridamole infusion.

2.3. PET scanning procedure

The PET scans were performed with an Ecat 931-08/12 15-slice tomograph (CTI/Siemens, Knoxville, TN, USA). The scanner enables the acquisition of 15 planes of data over a 10.5-cm axial field of view, allowing the whole heart to be imaged. All emission and transmission data were reconstructed with a Hanning filter with a cut-off frequency of 0.5 units of reciprocal of the sampling interval of the projection data, achieving an image resolution of 8.4×8.3×6.6 mm^3 full-width half maximum at the center of the field of view [20].

All subjects were asked to abstain from caffeine-containing beverages for 24 h before the scan. Blood was drawn for caffeine levels, which were nonmeasurable in all subjects tested prior to the study. Subjects were positioned in the scanner, and after exposure of a retractable ^{68}Ge ring source, a 5-min rectilinear transmission scan was acquired to determine the optimal imaging position of the left ventricle within the field of view. A 20-min transmission scan was subsequently performed for the purpose of attenuation correction of all emission scans. To maintain the optimal imaging position of the subject within the scanner, a low power laser beam was superimposed on a cross-shaped ink mark on the subject's chest and this position was kept constant throughout all the emission scans. Starting after a 30-s background frame, a bolus of $H_2^{15}O$ (700–900 MBq) was injected intravenously over 20 s at an infusion rate of 10 ml/min. The venous line was then flushed for another 2 min. The following scanning protocol was used: fourteen frames at 5 s, three frames at 10 s, three frames at 20 s, and four frames at 30 s, for a total scanning time of 310 s. The $H_2^{15}O$ bolus injection/scan was repeated after adenosine- or dipyridamole-induced hyperemia.

2.4. PET image processing

The acquired sinograms were corrected for attenuation and reconstructed on a Microvax II computer (Digital Equipment, Marlboro, MA, USA) using dedicated array processors and standard reconstruction algorithms. Images were then transferred to a Sun Sparc 2 workstation (Sun Microsystems, Mountainview, CA, USA). Images were analyzed with customized MATLAB software (The Mathworks Natick, MA, USA). Myocardial images were generated directly from the dynamic $H_2^{15}O$ study. Briefly, regions of interest defined in the lungs on the transmission image provided the required variate and covariate factors (the myocardial and blood time–activity curves) for modeling of factor sinograms by means of the recently reported linear dimension reduction [21,22]. Factor images were generated by iterative reconstruction [23]. Regions of interest were then drawn in the left atrium and right ventricle on four to six consecutive image planes and projected onto the dynamic $H_2^{15}O$ images to generate blood time–activity curves (arterial and venous input function). Similarly, four myocardial region of interest (septal, anterior, lateral and inferior) were drawn in the left ventricular myocardium on 12 consecutive planes and projected onto the dynamic $H_2^{15}O$ images to obtain tissue time–activity curves. Arterial, venous and tissue input functions were the fitted to a single tissue compartment tracer kinetic three-parameter model to give values of regional and global MBF (ml/min/g) as previously described [23,24]. When applied to the septum a four-parameter model was used in order to correct for the spillover from the right ventricle.

To account for the changes in MBF produced by cardiac workload, baseline MBF was also corrected for the rate pressure product (RPP), an index of myocardial oxygen consumption, using the formula: $MBF_{corr}=(MBF_{baseline}/RPP)\times10^4$. Coronary vasodilator reserve (CVR) was calculated as the ratio of $MBF_{ado/dip}$ to $MBF_{baseline}$. In addition, CVR was also calculated using baseline MBF corrected for RPP as $CVR_{corr}=MBF_{ado/dip}/MBF_{corr}$ [17].

2.5. Statistical analysis

All values are reported as mean±S.D. Statistical analysis was performed using the Statview package (SAS Institute, Cary, NC, USA). The coefficient of variation was used to demonstrate the degree of variability of MBF and CVR. A standard Wald-type test was used to compare the coefficients of variation between the first and second flow assessments at baseline and during hyperemia [25]. Paired *t*-tests were used to compare regional MBF within individuals at a single time point. Simple, multiple and polynomial regression were performed to assess the relationships between independent variables (age, gender, hemodynamic variables, stressor) and MBF and CVR. Gender comparison was performed between males and females after adjusting for age using the analysis of covariance. Simple regression analysis was also used to correlate repeated flow estimates at baseline and during hyperemia and to assess the relationship between baseline and hyperemic MBF. ANOVA means table and Fisher's post-hoc test were used to assess the relationship between gender and baseline and hyperemic MBF. ANOVA and Scheffé's posthoc test were used to assess differences in regional MBF of the whole group.

3. Results

All subjects tolerated the procedures well except for the common side effects of the adenosine or dipyridamole infusion, but none experienced chest pain or exhibited electrocardiographic changes suggestive of ischemia. For the whole group of 169 subjects, the mean resting heart rate was 63±10 (range 37–99) beats/min, systolic blood pressure 121±15 (range 90–171) mmHg, and diastolic blood pressure 72±10 (range 52–94) mmHg. The mean resting RPP was 7623±1689 (range 4488–14 157) mmHg×beat/min. Age was linearly associated with systolic ($P=0.0011$), diastolic ($P=0.0177$), and mean arterial pressure ($P=0.0083$) There was also a linear, but nonsignificant trend between age and RPP ($P=0.0900$).

At peak adenosine-induced hyperemia, the mean heart rate was 88±15 (range 44–122) beats/min, systolic blood pressure 122±16 (range 86–159) mmHg, diastolic blood pressure 68±10 (range 46–89) mmHg, and mean RPP was 10843±2596 (range 4224–18 178) mmHg×beat/min. At peak dipyridamole-induced hyperemia, the mean heart rate was 90±15 (range 60–131) beats/min, systolic blood pressure 126±17 (range 85–173) mmHg, diastolic blood pressure 70±10 (range 48–103) mmHg and mean RPP was 11 307±2463 (range 7200–19 030) mmHg×beat/min.

3.1. Baseline flow

The frequency distributions of global (i.e. mean flow in the whole left ventricle) MBF and MBF_{corr} are shown in Fig. 1. MBF was 0.985±0.230 ml/min/g (range 0.590–2.050 ml/min/g, coefficient of variation 27%) and MBF_{corr} 1.330±0.316 ml/min/g (range 0.736–2.428 ml/min/g, coefficient of variation 24%).

3.1.1. Effects of age and gender

MBF showed a significant linear association with age (Fig. 2, top), which is partly explained by the trend for an association between age and RPP. The latter is in turn significantly associated with MBF (Fig. 2, middle). In females MBF (1.182±0.251 ml/min/g) and MBF_{corr} (1.563±0.322 ml/min/g) were significantly higher than MBF (0.930±0.191 ml/min/g) and MBF_{corr} (1.265±0.284 ml/min/g) in males ($P<0.001$, for both

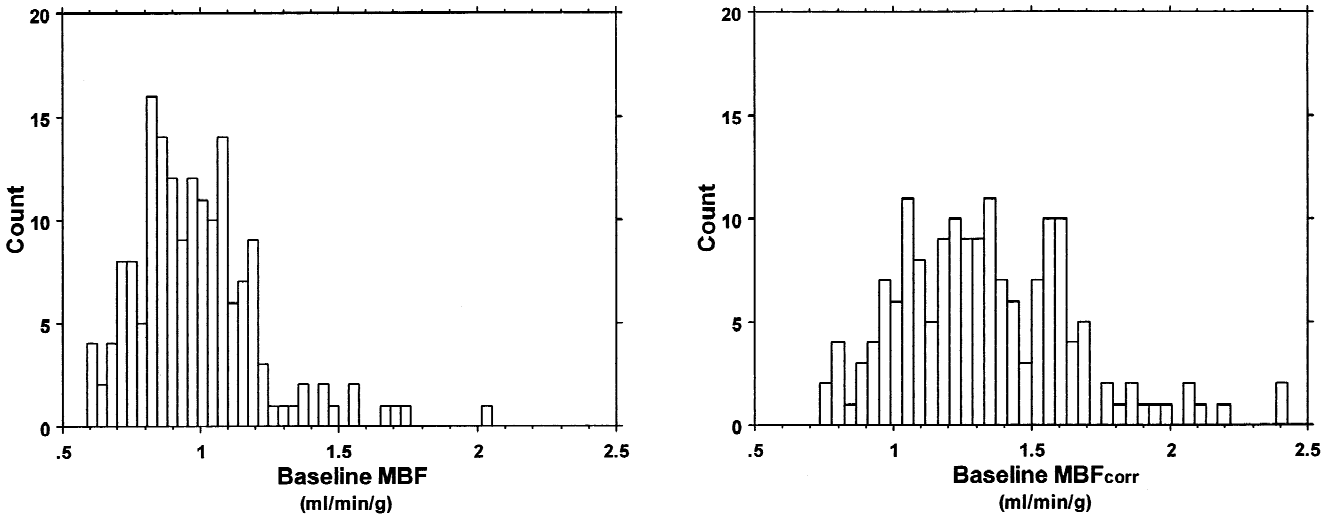

Fig. 1. Frequency distribution of (left) uncorrected baseline global MBF (coefficient of variation 27.1%) and (right) baseline global MBF_{corr} (coefficient of variation 24.0%).

comparison). The study population was skewed towards a larger number of males and older females. However, MBF in females remained significantly higher than in males ($P<0.0001$) after adjustment for age. Moreover, neither age nor the interaction between age and gender showed any significance after adjustment for gender ($P=0.81$). Regional flows were related to age in a manner similar to that observed for global flows and values were significantly higher in females in all segments (Table 1). After adjustment for age, gender remained significant ($P<0.0001$). Neither age nor the interaction between age and gender showed any significance after adjustment for gender for each region.

3.1.2. Spatial heterogeneity

The distribution of MBF_{corr} within each myocardial region in the whole study population is illustrated in Fig. 3. MBF_{corr} was 1.333 ± 0.329 ml/min/g in the septum, 1.443 ± 0.4113 ml/min/g in the anterior wall, 1.405 ± 0.385 ml/min/g in the lateral wall and 1.232 ± 0.322 ml/min/g in the inferior wall. The overall ANOVA P value for regional MBF_{corr} was <0.0001, with an F factor of 9.145. Posthoc analysis showed significant differences in MBF among the following segments: inferior vs. anterior ($P<0.0001$) and inferior vs. lateral ($P<0.0001$).

The true variability of baseline MBF was assessed by comparing paired estimates of regional baseline MBF within each individual at a single time point. There were significant differences in both uncorrected and corrected estimates of baseline myocardial blood flow among the following regions: anterior vs. inferior ($P<0.001$); anterior vs. septum ($P<0.001$); inferior vs. lateral ($P<0.001$); inferior vs. septum, ($P<0.001$); and lateral vs. septum ($P<0.001$), but not between anterior vs. lateral segments. The dispersion among these four regions may be summarized by the average coefficient of variation, which was $13\pm8\%$ for both uncorrected and corrected estimates of baseline flow.

3.1.3. Temporal heterogeneity

In the subgroup of 21 individuals undergoing repeated assessment of MBF, there was no significant difference between the coefficients of variation (19.1627 vs. 19.1913; P=NS) for the first and the second baseline MBF_{corr}. There was a good correlation between the two baseline MBF_{corr} measurements ($r=0.756$; $P<0.0001$). Moreover, for each region, the coefficients of variation between the first and second regional baseline MBF_{corr} were not significantly different.

3.2. Hyperemic flow

Global hyperemic MBF was 3.542 ± 1.010 ml/min/g (range 1.110–5.990 ml/min/g, coefficient of variation 29%).

3.2.1. Comparison between adenosine- and dipyridamole-induced hyperemia

Females received only dipyridamole for pharmacologic vasodilation while males received either dipyridamole or adenosine for reasons stated previously (see Methods). Therefore, the comparison of adenosine- vs. dipyridamole-induced hyperemia was performed only in males. Hyperemic MBF response to adenosine (mean 3.766 ± 0.854, range 1.851–5.990) was significantly ($P=0.0114$) higher than that to dipyridamole (mean 3.107 ± 1.120, range 1.100–5.270) at these doses of stressors.

3.2.2. Effects of age and gender

Gender differences in hyperemic MBF were tested only for dipyridamole-induced hyperemia. The gender differ-

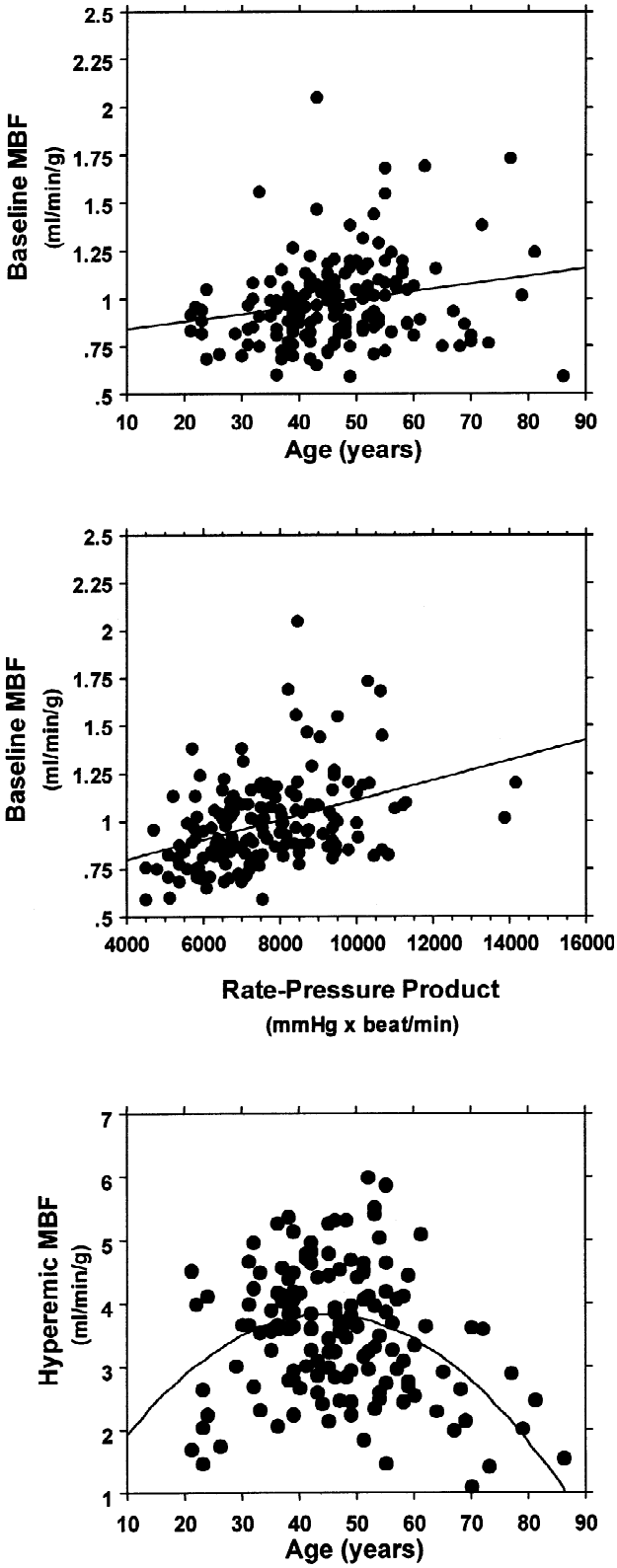

Fig. 2. Scatterplot showing the relationship between (top) age and uncorrected baseline global MBF ($y = 0.803 + 0.004x$; $r = 0.21$; $P = 0.0086$, (middle) RPP and uncorrected baseline global MBF ($y = 0.593 + 5.217 \times 10^{-5}x$; $r = 0.39$; $P < 0.0001$) and (bottom) age and hyperemic global MBF ($y = 0.666 + 0.142x - 0.002x^2$; $r = 0.41$; $P < 0.0001$). The data points in the bottom panel illustrate the lower hyperemic MBF in subjects older than 55 years. In the few youngest subjects (six of nine), hyperemic MBF was also lower than the mean for the group.

Table 1
Segmental MBF in females and males[a]

Region	Uncorrected MBF (ml/min/g)			Corrected MBF (ml/min/g)		
	Females	Males	*P*	Females	Males	*P*
Septum	1.178±0.351	0.930±0.206	<0.0001	1.519±0.314	1.281±0.322	0.0002
Anterior	1.345±0.421	0.980±0.260	<0.0001	1.738±0.411	1.357±0.378	<0.0001
Lateral	1.343±0.457	0.956±0.196	<0.0001	1.720±0.430	1.308±0.270	<0.0001
Inferior	1.089±0.324	0.859±0.192	0.0001	1.403±0.284	1.178±0.315	0.0002

[a] Data are expressed as mean±standard deviation.

ence observed for baseline MBF was not present for hyperemic MBF. There also appears to be a quadratic relation between age and hyperemic MBF (Fig. 2, bottom) with flows lower than the group's mean in subjects older than 55 years and in few youngest subjects (six of nine).

3.2.3. Spatial heterogeneity

Similarly to baseline, regional hyperemic MBF showed a considerable range of responses: septum, 0.915–7.305; anterior, 1.150–8.134; lateral, 1.050–7.153; and inferior, 0.750–6.980 ml/min/g. The histogram in Fig. 4. top illustrates the broad range of distribution of regional hyperemic flow in the whole population. However, there were no statistically significant differences (ANOVA) in hyperemic MBF among the four myocardial regions. The true spatial heterogeneity for each individual at a single time point was shown by the statistically significant difference in MBF between the inferior wall and all the other regions ($P<0.001$ in each case). The dispersion was slightly greater than for baseline MBF with a coefficient of

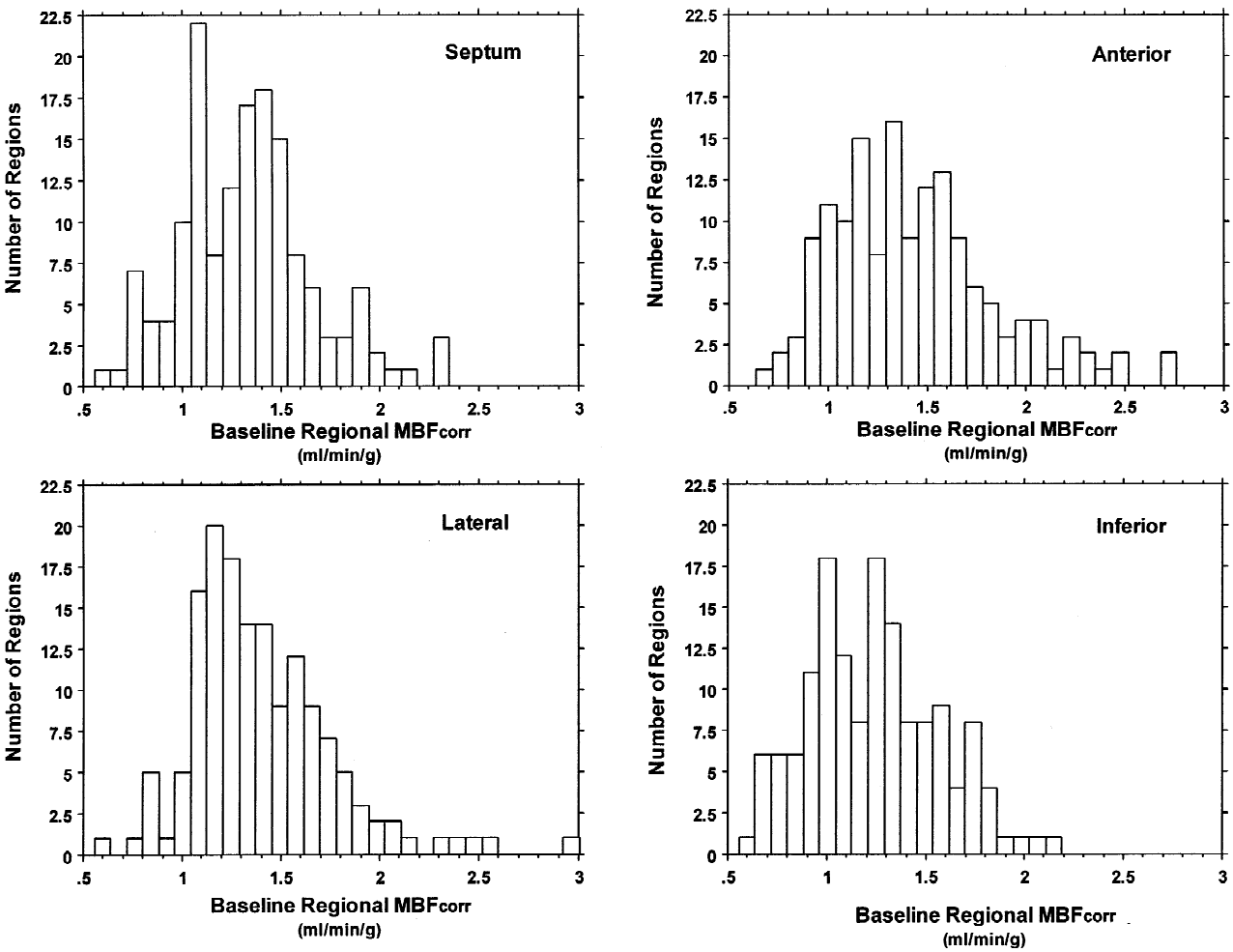

Fig. 3. Histogram of corrected baseline regional MBF. The coefficient of variation for each segment was: septum, 24.7%; anterior, 28.6%; lateral, 25.3% and inferior 26.1%.

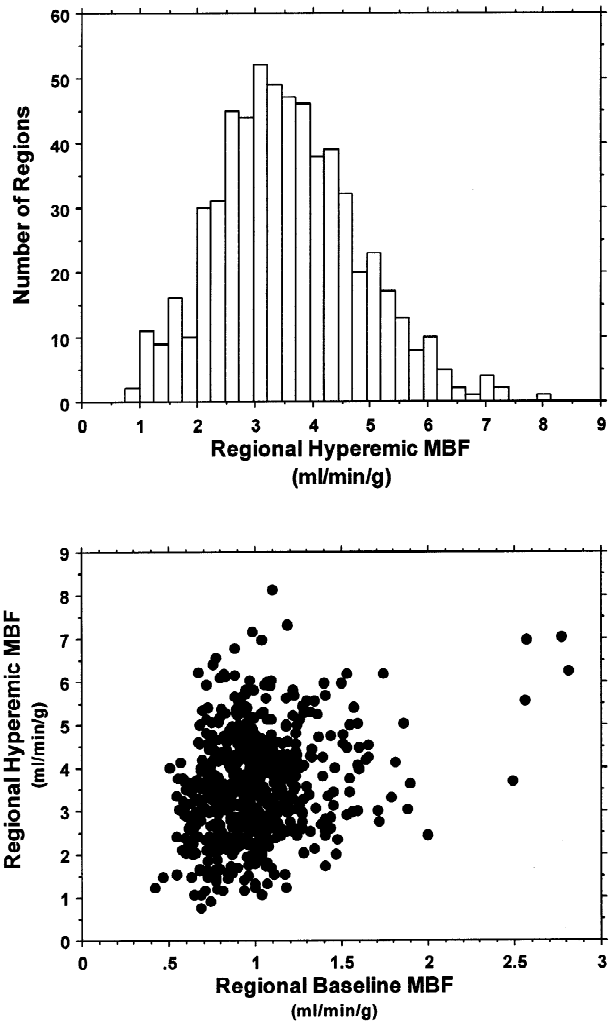

Fig. 4. Histogram showing the distribution of hyperemic regional MBF in the population (top). The coefficient of variation was 34.1%. Scatterplot (bottom) comparing baseline MBF hyperemic MBF for the same region demonstrates a lack of correlation between baseline and maximal flow patterns ($r=0.23$; $P=$NS).

variation of 17±10%. To test whether the hyperemic response was related to baseline MBF, we compared baseline and hyperemic MBF in the same regions. Fig. 4, bottom illustrates the lack of correlation between baseline and hyperemic MBF in each region ($r=0.23$; $P=$NS). In other words, regions with a higher baseline flow were not more likely to have higher hyperemic response than regions with a lower baseline flow.

3.2.4. Temporal heterogeneity

In the 21 individuals undergoing repeated assessment of MBF, there was no significant difference between the coefficients of variation (23.6534 vs. 25.2366; $P=$NS) for the first and the second hyperemic MBF. Likewise there were no regional differences in the coefficients of variation for hyperemic flows.

3.3. Coronary vasodilator reserve

Global CVR with adenosine and dipyridamole showed a wide range of responses from 1.360 to 8.130 (mean 3.753±1.240) for uncorrected and from 1.020 to 6.300 (mean 2.794±0.947) for corrected (Fig. 5). The relationship between age and CVR follows a similar pattern observed for age and hyperemic MBF (Fig. 2, bottom). There was also a wide distribution of regional CVR_{corr}. There was no significant difference in either uncorrected or corrected CVR among different regions.

4. Discussion

In the present study, we have investigated the limits of MBF in a large population of healthy males and females over a broad range of ages. We specifically selected human subjects with a low likelihood for coronary artery disease [18]. The results can be summarized as follows. (1) In this

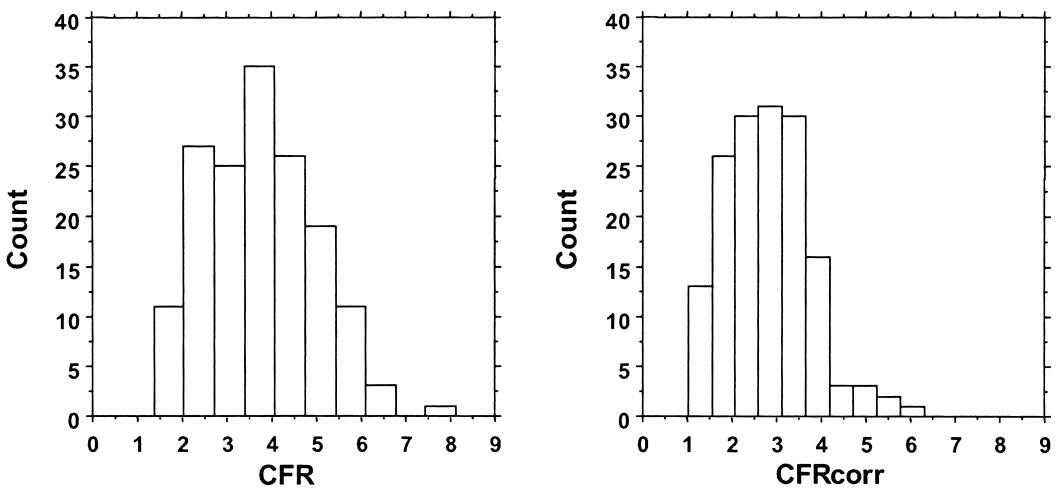

Fig. 5. Histogram showing the distribution of uncorrected (left) and corrected (right) CVR. The coefficient of variation was 33.0 and 33.9%, respectively.

population, baseline and hyperemic MBF are heterogeneous both within and between individuals. Baseline and hyperemic MBF exhibit a similar degree of spatial heterogeneity which appears to be temporally stable. (2) Baseline, but not hyperemic, MBF is significantly higher in females than in males. (3) There is a significant linear association between age and baseline MBF that is in part related to changes in external cardiac workload with age. (4) Hyperemic MBF declines over 65 years of age. (5) At the doses employed in the present study, adenosine-induced hyperemic MBF is significantly higher than dipyridamole-induced hyperemic MBF.

Our results are in agreement with previous animal and human studies [7,11–13,26–29] that have provided evidence for significant heterogeneity of global and regional baseline MBF. A number of considerations suggest that this heterogeneity reflects a true biologic phenomenon. First, there is spatial heterogeneity of MBF within each individual to support the overall variability of global MBF. Second, the degree of spatial heterogeneity exhibited in this study is similar to that found in animal [6,8,10–12,30,31] and smaller human [13,26,27] studies using different methods with different spatial resolution to estimate MBF, suggesting that our observation is not a methodological artifact. Third, this spatial heterogeneity exhibits remarkable temporal stability. Fourth, the temporal variability of PET is small as demonstrated by the high repeatability of MBF measured 20 min apart in the same subjects [17].

Both temporal and spatial heterogeneity of MBF have been described in animals [10], however, the underlying physiologic mechanism for the heterogeneity of baseline MBF in humans remains ill defined. We have already demonstrated [17] that PET estimates of MBF are reproducible over time. Small temporal fluctuations in baseline MBF may be attributed to 'twinkling' of capillary flows [30] and/or time-dependent changes in regional metabolic requirements coupled to local autoregulatory changes in blood flow [6,8,32]. In addition, the spatial heterogeneity of MBF may be also attributed to the fractal nature of regional flow distribution [33,34] and different neural regulatory modulation in different regions and layers of the left ventricle [10,32]. Differences in transmural MBF distribution across the left ventricle [35–39] may also contribute to the spatial heterogeneity although their magnitude is smaller than the overall heterogeneity [32].

As demonstrated by our results, the inter-individual variability of hyperemic MBF is even greater than that observed for baseline MBF. Both age and the type of vasodilator used determine the degree of hyperemia achieved and thus are sources of variability. Therefore, these factors need to be considered when comparisons of different populations are performed. On the other hand, the intrinsic variability due to spatial heterogeneity within the same hearts was found to be limited to a consistently lower flow in the inferior wall.

In conscious primates, the heterogeneity of MBF before coronary occlusion can explain the variability in myocardial salvage following reperfusion. The presence of higher precoronary occlusion resting MBF may predict the propensity for infarction in that region [12]. In our investigation of normal humans, baseline MBF did not predict hyperemic MBF in the same region. The result is a wide range of regional CVR, which has important clinical implications. Measurements of regional CVR of less than 2.5 are often interpreted as impaired vasodilator capacity. However, in our population of normal volunteers, many left ventricular segments have a CVR, both uncorrected and RPP-corrected, of less than 2.5. This distribution of both MBF and CVR must be recognized before defining these parameters as abnormal. These findings may also explain, at least in part, the patchy distribution of myocardial injury within a given region and suggests that there may be regions operating near maximal capacity in the baseline state, becoming more susceptible to injury when demand exceeds supply [12].

4.1. Aging, myocardial blood flow and coronary vasodilator reserve

The influence of age on baseline MBF has been previously investigated by our and other groups with PET [13,28,40]. The results of the present study confirm that baseline MBF increases linearly with age with greater heterogeneity of baseline MBF in the oldest individuals (Fig. 2, top). Furthermore, the linear association between age and baseline MBF seems to be explained in part by the linear association between age and RPP.

In agreement with previous studies [26,28,41–43] we find that hyperemic MBF declines with increasing age (Fig. 2, bottom). Therefore, in subjects older than 65 years, the combination of the increase in baseline and reduction in hyperemic MBF leads to an even larger decrease in CVR. These changes are likely to results from the combination of a number of mechanical and neurohumoral factors associated with aging including increased arterial impedance, thickening of left ventricular myocardium, reduced lusitropism, reduced catecholamine-responsiveness, endothelial dysfunction and deficient neuroendocrine regulation [26,44–46]. We believe that this decrease in CVR is a true phenomenon since other investigators, using different techniques, have found similar results. With regard to the apparent reduction in hyperemic MBF in the youngest individuals (Fig. 2C), it is worth noting that because of the limitations due to ethical issues, only a small number of subjects were studied. Therefore, we cannot rule out a sampling bias, although the fit of the curve is statistically significant. Finally, there are no data on whether aging modulates the pharmacological effects of dipyridamole and adenosine, but it is conceivable that peak vasodilation could occur at different times in younger than in older individuals.

4.2. Gender, myocardial blood flow and coronary vasodilator reserve

We and others have previously reported gender differences in baseline MBF [28,47,48]. The present investigation in a larger population confirms that baseline MBF is higher in females even after RPP correction. Although in the whole study population the mean age of females was significantly higher than that of males, after adjustment for age, the influence of gender on baseline MBF remained significant. This difference can be explained, at least in part, by the well known effects of estrogens on vascular tone in female subjects with coronary artery disease [49].

Using dipyridamole as vasodilator, we found higher hyperemic flow in females than in males although this difference fell short of statistical significance. Similar findings were noted in previous studies using the same protocol of dipyridamole infusion in syndrome X patients, and using either adenosine or dipyridamole infusion in normal subjects [28,47]. While females in our study had slightly higher hyperemic flow than males, their CVR was overall lower than in males due to the females' higher baseline flow. The latter point should be taken into account when assessing CVR in females.

4.3. Hyperemic response and stressor

In our group of normal men, adenosine at a dose of 140 μg/kg/min appears to induce a slightly greater hyperemia than dipyridamole at a dose of 0.56 mg/kg although there was considerable overlap of hyperemic response between the two agents. In a previous study with PET, MBF hyperemic response was measured twice with both adenosine and dipyridamole in 20 normal men and no significant difference in the level of hyperemia was detectable between the two agents [40]. This disagreement could be due to a variance of inter-individual responsiveness to inhibition of phosphodiesterase and/or density of A_2 receptors. Therefore it can be assumed that the two drugs are equipotent in the same subject, but direct stimulation of A_2 receptors with adenosine is more likely to induce in the majority of cases maximal vasodilatation.

4.4. Limitations of the study

The present study has several potential limitations. (1) Although this group of subjects was carefully screened for coronary artery disease and was at low-risk by history, physical examination, and laboratory results, asymptomatic coronary artery disease may still exist, particularly in the older adults. A coronary angiogram would provide definitive data, but ethical considerations restrain invasive diagnostic in healthy subjects. CVR assessment, however, revealed no evidence of regional deficits in any of the subjects, making the presence of hemodynamically significant coronary stenoses unlikely. Similarly, we cannot completely rule out age-related changes in ventricular function and morphology, which may result in an abnormal flow reserve, although there were no electrocardiographic abnormalities suggesting underlying pathology. Along these lines, it is beyond the scope of this study to determine whether the lack of response to coronary vasodilator stimuli in the absence of coronary artery disease is a true biological phenomenon in some individuals. Since there are reports that the standard dose of dipyridamole (0.56 mg/kg) does not consistently produce maximal vasodilatory effect in all individuals [42], it is conceivable that there are nonresponders, perhaps as a result of operating near maximal capacity at baseline [12], differences in dietary influences [50], or variations in the pharmacological effects of these vasodilator stimuli. Although patients were instructed not to consume caffeine-containing foods and beverages prior to the study, we did not measure caffeine levels in all patients, leaving a possibility of a blunted vasodilator effect due to the presence of xanthines. (2) Our population was skewed towards fewer and older females. Nevertheless, we were able to perform meaningful statistical analyses on this distribution of females and males. Unfortunately, we did not have the estrogen status of the female subjects in this study and therefore could not provide further analyses on the effects of estrogen on MBF and delineate whether estrogen is the mechanism of higher flow in women than in men. (3) The resolution of the scanner in this study does not permit evaluation of smaller regions of interest, which may provide a closer insight into the mechanisms underlying the observed flow variability. In particular, it was not within the scope of this study to differentiate as to whether the observed reduction in flow to the inferior wall compared to other regions is a true biological phenomenon or a methodological artifact. However, a lower basal average peak velocity measured by Doppler-tipped guide wire has previously been observed [51], suggesting the possibility that the lower inferior baseline flow may be a true biological phenomenon. Furthermore, since baseline flow is closely coupled to myocardial workload and oxygen consumption, it could be hypothesized that these differences in regional blood flow are the consequence of parallel differences in workload and oxygen consumption. Unfortunately, in our study, we did not assess regional workload nor oxygen consumption, and therefore we cannot prove whether this hypothesis is correct. A number of methodological reasons could also account, at least in part, for the observed regional changes. Most importantly, changes in regional wall thickness could result in different partial volume effects and count recovery. However, since our data are corrected for partial volume, this does not seem to be the reason. Finally, different amounts of spillover from neighboring organs with high activity such as liver or spleen may have a more significant impact on the inferior wall.

5. Conclusions

The results of the present investigation confirm and extend previous findings on the variability of baseline and hyperemic MBF in humans. Our results demonstrate that a number of factors including age, gender, cardiac workload and type of vasodilator drug must be taken into account when considering the limits of distribution of MBF in normal human subjects. These data have important implications for the interpretation of myocardial perfusion studies in patients and the understanding of the pathophysiology of hibernating myocardium.

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